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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/086,169	Applicant(s) RABINDRAN ET AL.	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-28,57-59,61 and 63* is/are pending in the application.

4a) Of the above claim(s) *34-38,61 and 63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-28 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This application is a division of 09/321182 which claims priority from Provisional Application 60/109,801.

The parent application 09/792,801 appears to provide adequate support under 35 U.S.C. 112 for the claims in this application.

Applicant's preliminary amendment submitted February 28, 2002 in the instant application in Paper No. 4 is acknowledged, wherein the instant specification has been amended as to add the priority information in the beginning of the specification, and claims 1-12, 29-33, 39-56, 60 and 62 are cancelled, and claims 57-59, and 61 have been amended.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, Claim 13-28 and 57-59 in Paper No. 6, submitted May 3, 2003 is acknowledged. On consideration by the examiner, the Restriction Requirement is modified to three inventions as follows,

I. Claims 13-28 and 57-59 drawn to methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance, comprising administration of an effect amount of the

specified agent herein, classified in class 514, subclass 410, 411, and 415 for example.

II. Claims 34-38 and 61 drawn to methods of treatment of BCRP or other non-P-gp/non MRP multiple drug resistance comprising administration of an effect amount of the specified agent herein, classified in class 514, subclass 410, 411, and 415 for example.

III. Claim 63 drawn to a culture of the organism Aspergilus fumigatus having the identifying characteristics of LL-S266 herein, classified in class 514, subclass 410, 411, and 415 for example.

Thus, Group I - III are unrelated to each other. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01. In the instant case the inventions are separate and distinct each from the other because they have different functions. The invention of Group I functions to distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and to determine the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance. The invention of Group II functions to treat BCRP or other non-P-gp/non MRP multiple drug resistance. The invention of Group III is drawn to a culture of the organism Aspergilus fumigatus having the identifying characteristics of LL-S266 herein. Therefore, Group I - III have different functions and different modes of operation.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 34-38, 61, and 63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 13-28 and 57-59 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-14, 17-19, 21, 23-25 and 28 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular chemotherapeutic agents herein disclosed in the claim, i.e., claims 15 and 26 and the specification (e.g., page 3) and the particular chemosensitizing reversal agents of formula I herein disclosed in the claim, i.e., claims 57-59 or fumitremorgin A, B, C, employed in the claimed methods herein for distinguishing the multiple drug resistance herein, does not reasonably provide enablement for the employment any chemotherapeutic agents and any

chemosensitizing reversal agents employed in the claimed methods of the particular treatments herein.

These recitations, "a chemotherapeutic agent" and "a chemosensitizing reversal agent" in the claims are seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance, comprising administration of an effect amount of the specified agent herein.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims 13-14, 17-19, 21, 23-25 and 28 are deemed very broad since these claims read on any chemotherapeutic agents and any chemosensitizing reversal agents employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 13-14, 17-19, 21, 23-25 and 28, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, "a chemotherapeutic agent" and "a chemosensitizing reversal agent", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for each kind of functional compounds for the claimed method of treatment herein.

Thus, Applicants' functional language at the points of novelty in claims herein fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph.

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treatment herein, side effects, and serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (i.e., cancer cells) any compounds represented by "a chemotherapeutic agent" and "a chemosensitizing reversal agent".

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties herein to be administered to a host for the claimed methods herein of the treatment.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that the testing herein merely employed the particular the particular chemosensitizing reversal agents of formula I herein or fumitremorgin A, B, C, (see Table 14 at page 30 of the specification). Additionally, it is noted what one particular chemotherapeutic agent, mitoxantrone, was tested in the combination with the particular chemosensitizing reversal agent described in page 16-30 of the specification.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure

of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expressions "**R7** NH(CH2)v or ..." and "**R7** is H or ...", and "**R8** is selected from ..." in claims 57-59 renders claims 57-59 indefinite. The expressions "**R7** NH(CH2)v or ..." and "**R7** is H or ...", and "**R8** is selected from ..." are not understood since there are no R7 and R8 in the formula I. Therefore, the scope of claims is indefinite as to the method encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-15, 17-20, 23-26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Abe et al. (Br. J. Cancer, 1995, 72, page 418-423, PTO-1449).

Abe et al. discloses the method of determining the chemosensitization of spontaneous multidrug resistance (i.e., the overexpression of MRP/p-gp or MDR1) in human cancer cells exhibiting such resistance comprising administering an effective amount of a chemosensitizing reversal agent such as verapamil in combination with a chemotherapeutic agent such as doxorubicin, concurrently, and the. See Abe et al., the entire article particularly Summary, page 418. The method of Abe et al. inherently distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and determine the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance since Abe's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389. Thus, the administration of the same active agents inherently treat the same cancer cells under the doctrine of inherency. See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881

(Fed. Cir. 2001) with regard to inherency as it related to the claimed invention herein. Thus, Abe et al. anticipates claims 13-15, 17-20, 23-25 and 28.

Claims 13-14, 17-19, 23-25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Tasaki et al. (J. Urology 1995, 154, page 1210-1216, PTO-1449).

Tasaki et al. discloses the method of reversal the non-P-gp-mediated multidrug resistance in human prostatic cancer cells exhibiting such resistance comprising administering an effective amount of a chemosensitizing reversal agent such as a 1,4-dihydropyridine derivative (NIK250) in combination with a chemotherapeutic agent such as etoposide, prior to, concurrently with or after administration. See Tasaki et al., the entire article particularly abstract and page 1210. The method of Tasaki et al. inherently distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and determine the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance since Tasaki's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389. Thus, the administration of the same active agents inherently treat the same cancer cells under the doctrine of inherency. See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001) with regard to inherency as it related to the claimed invention herein. Thus, Abe et al. anticipates claims 13-14, 17-19, 23-25 and 28.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-28 and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (Br. J. Cancer, 1991, 63, page 923-929, PTO-1449) and Cui et al. (PTO-892).

Taylor et al. discloses that the particular chemotherapeutic agent such as doxorubicin and mitoxantrone is known to be useful in the method of human breast cancer. See Taylor et al. the entire article particularly Summary and page 923.

Cui et al. discloses that the particular agents, fumitremorgin C or diketo piperazine derivatives from Aspergillus are neoplasm inhibitors, and are hence useful in the treatment of tumor and/or cancer. See abstract).

The prior art does not expressly disclose the employment of the particular chemotherapeutic agent such as doxorubicin and mitoxantrone in combination with the particular chemosensitizing reversal agent herein in methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ of the particular chemotherapeutic agent such as doxorubicin and mitoxantrone in combination with the particular chemosensitizing reversal agent herein in methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ of the particular chemotherapeutic agent such as doxorubicin and mitoxantrone in combination with the particular chemosensitizing reversal agent herein in methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance since doxorubicin or mitoxantrone, and fumitremorgin C or diketo piperazine derivatives from Aspergillus, are known to be useful in a method of treating particular cancer based on the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that combining doxorubicin or mitoxantrone, and fumitremorgin C or diketo piperazine derivatives from Aspergillus known useful for the same purpose in a composition to be administered would improve the therapeutic effect for treating particular cancer.

Since all active composition components herein are known to useful to treat particular cancers, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
July 7, 2003